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A HYPOGLYCEMIC AGENT

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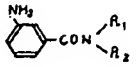
Specification

1. Title of Invention

A hypoglycemic agent.

2. Patent Claims

A hypoglycemic agent containing as effective component a compound represented by general formula

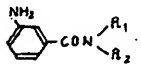


[I]

(wherein, R_1 and R_2 may be the same or different and denote a hydrogen atom, a straight-chain, branched-chain or cyclic alkyl group, an aralkyl group which can have a substituent in the nucleus, or a phenyl group which may be substituted).

3. Detailed explanation of the invention

This invention is a hypoglycemic agent containing as effective component a compound represented by general formula



[I]

(wherein, R_1 and R_2 may be the same or different and denote a hydrogen atom, a straight-chain, branched-chain or cyclic alkyl group, an aralkyl group which can have a substituent in the nucleus, or a phenyl group which may be substituted).

Among the compounds represented by aforesaid formula [I], a well known compounds are included, however, hypoglycemic action or a pharmacological action that suggests this are not described whatsoever in the prior publications describing those compounds.

The compounds represented by aforesaid formula [I] can be easily obtained for example by reduction by conventional method of corresponding meta-nitrobenzoic acid amide species as shown in the Reference Example below.

Reference Example

Into a mixed solution of 6 g isopropylamine, 15 ml triethylamine and 200 ml acetone was gradually added 18.6 g meta-nitrobenzoyl chloride under ice cooling and stirring. the mixture was stirred at the same temperature for 30 minutes and then at room temperature for one hour, thereafter, the reaction liquor was discharged into 1 litre of water, precipitated crystals were recovered by

filtration, washed with water, thereafter recrystallised, and meta-nitro-N-isoproylbenzamide (m.p. 131-132°C) 18.7 g was thereby obtained as colourless acicular crystals. Hydrogen was passed though a mixed liquor of 5.2 g of said amide, 0.5 g of 10 % palladium-carbon and 100 ml ethanol, and catalytic reduction was carried out by conventional method. After theoretical quantity hydrogen was absorbed, catalyst was eliminated, the reaction liquor was concentrated under reduced pressure, the residue was recrystallised from ethanol, and thereby meta-amino-N-isoproyl benzamide (compound 1) 4.1 g was obtained as colourless acicular crystals. m.p. 148-149°C.

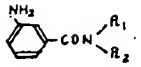
Elemental analysis: as molecular formula $C_{10}H_{14}N_2O$

	C	H	N
Calculated values (%)	67.38	7.92	15.72
Measured values (%)	67.35	7.94	15.69

Compounds of Table 1 were obtained in the same way as above.

wherein, compounds 25, 27 and 29 were obtained as oily substances, the value of high mass spectra are shown in the Table and the NMR values are shown below the Table.

Table 1



[I]

Comp. No.	Substituent and position R_1	R_2	Molecular formula	m.p. (°C)	Yield (%)	Elemental analysis value Calc. (%) C	H	N	Measured (%) C	H	N
2	H	H	$C_7H_8N_2O$	77~78	81	61.75	5.92	20.58	61.71	5.96	20.55
3	〃	CH_3	$C_8H_{10}N_2O$	121~122	85	63.98	6.71	18.65	63.92	6.68	18.69
4	〃	C_2H_5	$C_9H_{12}N_2O$	70~71	76	65.83	7.37	17.06	65.72	7.28	17.19
5	〃	n-C_3H_7	$C_{10}H_{14}N_2O$	57~58	76	67.38	7.92	15.72	67.25	7.88	15.64
6	〃	n-C_4H_9	$C_{11}H_{16}N_2O$	112~113	75	68.72	8.39	14.57	68.70	8.37	14.50
7	〃	sec-C_4H_9	〃	109~111	74		〃		68.67	8.44	14.65
8	〃	t-C_4H_9	〃	126~127	79		〃		68.69	8.36	14.51
9	〃	i-C_4H_9	〃	87~89	76		〃		68.75	8.46	14.62
10	〃		$C_{13}H_{16}N_2O$	147~148	84	71.52	8.31	12.83	71.58	8.35	12.76
11	〃		$C_{12}H_{12}N_2O$	132~133	86	72.56	5.70	13.20	73.50	5.67	13.26
12	〃		$C_{14}H_{14}N_2O$	88~89	84	74.31	6.24	12.38	74.24	6.20	13.45

Comp. No.	Substituent and position R_1	R_2	Molecular formula	m.p. (°C)	Yield (%)	Elemental analysis value Calc. (%) C	H	N	Measured (%) C	H	N
13	H		$C_{16}H_{16}N_2O_3$	83~84	76	66.15	5.92	10.29	65.98	5.88	10.35
14	〃		$C_{14}H_{13}N_3O_2$	180~182	56	65.87	5.13	16.46	65.75	5.18	16.55
15	〃		〃	135~136	59		〃		65.79	5.10	16.52
16	〃		〃	223~226	68		〃		65.81	5.07	16.53
17	〃		$C_{13}H_{13}N_3O$	151~153	79	68.70	5.77	18.49	68.64	5.79	18.43
18	〃		〃	130~131	71		〃		68.77	5.70	18.53
19	〃		〃	150~151	74		〃		68.75	5.67	18.42
20	〃		$C_{14}H_{12}N_2O_3$	231~233	59	65.62	4.72	10.93	65.71	4.66	11.02
21	〃		$C_{14}H_{14}N_2O$	96~97	73	74.31	6.24	12.38	74.25	6.19	12.49
22	〃		$C_{15}H_{16}N_2O$	94~95	80	74.97	6.71	11.66	74.92	6.75	11.61
23	〃		$C_{15}H_{16}N_2O_2$	109~110	79	70.29	6.29	10.93	70.34	6.32	10.89
24	〃		$C_{14}H_{13}ClN_2O$	131~132	67	64.49	5.03	10.75	64.42	5.00	10.79

Comp. No.	Substituent and position R_1	R_2	Molecular formula	m.p. (°C)	Yield (%)	Elemental analysis value Calc. (%) C	H	N	Measured (%) C	H	N
25	H	$-CH_2CH_2-$⬡	$C_{18}H_{18}N_2O$	oil	62	ハイマスペクトル 240.1259			240.1246 (※1)		
26	CH_3	CH_3	$C_9H_{12}N_2O$	87~88	82	65.83	7.37	17.06	65.78	7.41	17.12
27	n-C_3H_7	n-C_3H_7	$C_{13}H_{20}N_2O$	oil	76	ハイマスペクトル 220.1571			220.1580 (※2)		
28	i-C_3H_7	i-C_3H_7	〃	179~180	80	70.87	9.15	12.72	70.79	9.15	12.78
29	n-C_4H_9	n-C_4H_9	$C_{18}H_{34}N_2O$	oil	74	ハイマスペクトル 248.1883			248.1875 (※3)		
30	i-C_4H_9	i-C_4H_9	〃	85~86	79	72.54	9.74	11.28	72.48	9.79	11.34

※1 : NMR ($CDCl_3$) δ : 7.55~6.40 (10H, aromatic-H, -CONH-), 3.75 (2H, s, $-NH_2$), 3.45 (2H, t, J=6Hz, $-OH_2$-), 2.75 (2H, t, J=6Hz, $-OH_2$-)

※2 : NMR ($CDCl_3$) δ : 7.35~6.50 (4H, aromatic-H), 3.90 (2H, s, $-NH_2$), 3.30 (4H, t, J=6Hz, ($-CH_2CH_2CH_3$)×2), 1.60 (4H, sextet, J=6Hz, ($-CH_2CH_2CH_3$)×2), 0.85 (6H, t, J=6Hz, ($-CH_2CH_2CH_3$)×2)

※3 : NMR ($CDCl_3$) δ : 7.15~6.40 (4H, aromatic-H), 4.00 (2H, s, $-NH_2$), 3.30 (4H, br, ($-CH_2CH_2CH_2CH_3$)×2), 1.40 (8H, br, ($-CH_2CH_2CH_2CH_3$)×2), 0.90 (6H, br, ($-CH_2CH_2CH_2CH_3$)×2)

The compounds of this invention obtained in this way have excellent insulin biosynthesis promotion action and hypoglycemic action, and are useful at 0.1-100 mg/kg with respect to human, and the effect thereof can be sustained for 24 hours or more by the administration of 0.1-100 mg/kg once a day.

For administration, preparations formed into desired agent form by conventional means used for normal formulation method are used.

Example 1

5-week-old DDY mice (males, body weight 25-30 g) comprising 5 animals per group were fasted for 16 hours, thereafter, aqueous solution or suspension of compounds of this invention (200 mg/kg) was orally administered, and 20 minutes later, streptozotocin 200 mg/kg was intravenously administered. Blood was collected from the heart on 24 hours later, blood sugar quantity was measured by glucose oxidase method and the plasma insulin quantity was measured by two antibody method. The measurement results are shown in Table 2.

Wherein, the compound number in the Table corresponds to the compound number of Reference Example.

Table 2

Administered compound	Blood glucose (mg/dl) mean ± S.E.M.	Plasma Insulin (μU/ml) mean ± S.E.M.
Normal mouse	157±6	199±40
None (control)	386±21	43±25
1	224±19 ***	176±37 *
2	157±16 ***	153±46
3	260±33 *	213±48 *
4	248±47 *	192±54
10	263±36 *	201±38 *
12	265±32 *	253±56 *
18	166±35 ***	190±51 *
21	150±6 ***	224±30 ***
24	193±41 **	173±63
25	210±39 **	184±48 *
26	267±53	220±37 **

*: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$

Example 2

meta-aminobenzamide (compound 2)	100 pts.
calcium hydrogenphosphate	58.5 pts.
crystalline cellulose	50 pts.
corn starch	40 pts.
calcium stearate	1.5 pts.

Above components were thoroughly mixed, and tablets, 250 mg per tablet (containing 100 mg effective component) was formed by conventional method. This is used as a hypoglycemic agent.

Example 3

A 40 % aqueous solution of meta-aminobenzylbenzamide (compound 21) was prepared, and 2 ml each thereof was sealed into ampoules and sterilised. This is used as a hypoglycemic injection.

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